Dept.: Chemical

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Serial No. 10/736,711

In the matter of the Application of: Johann LEBAN, et al.

For: COMPOUNDS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS

Due Date: n/a

The following has been received in the U.S. Patent Office on the date stamped hereor

- Dep. Acct. Order Form
- PTO Cover Letter
- Amendment Under 37 CFR 1.312

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Docket No.: 246883US0

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/736,711
Applicants: Johann LEBAN, et al.
Filing Date: December 17, 2003
Allowed Date: January 24, 2006
For: COMPOUNDS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS
Group Art Unit: 1621
Examiner: S. Kumar

SIR:

Attached hereto for filing are the following papers:

Amendment Under 37 CFR 1.312

Our check in the amount of **$0.00** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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DOCKET NO: 246883US0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
JOHANN LEBAN, ET AL.	: EXAMINER: KUMAR, S.
SERIAL NO: 10/736,711	: ALLOWED DATE: JANUARY 24, 2006
FILED: DECEMBER 17, 2003	: GROUP ART UNIT: 1621
FOR: COMPOUNDS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS	:

AMENDMENT UNDER 37 C.F.R.§1.312

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This application has been allowed, but the issue fee, as yet, has not been paid. Kindly make the following corrections to the claims.

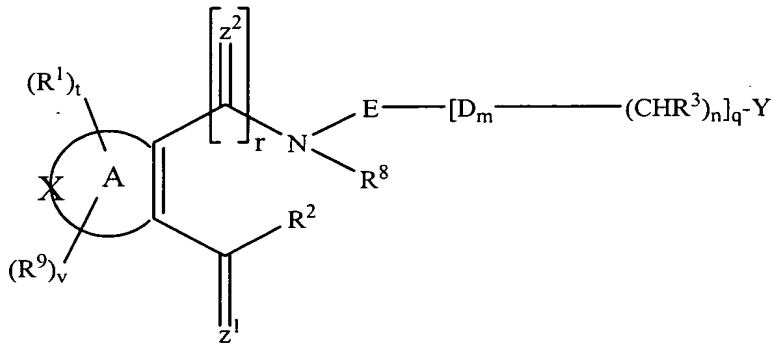
Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 13 of this paper.

IN THE CLAIMS

Please amend the claims as follows:

Claim 1 (Currently Amended): A compound of the general formula (I) or a salt or a physiologically functional derivative thereof:



(I)

wherein

A is a non-heterocyclic non-aromatic ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring represented by X may optionally be carbonyl (C=O);

D is O, S, SO_2, NR^4 or CH_2;

[[Z]] z^1 and [[Z]] z^2 are, independently, O, S, or NR^5;

R^1 is independently $-CO_2R''$, $-SO_3H$, $-CONR^*R''$, $-CR''O$, $-SO_2-NR^*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, -OH, -SH, alkylthio, $-NR''-CO_2-R'$, $-NR''-CO-R^*$, $-NR''-SO_2-R'$, $-O-CO-R^*$, $-O-CO_2-R^*$, $-O-CO-NR^*R''$, cycloalkyl, alkylamino, hydroxyalkylamino, aryl, or heteroaryl;

R^9 is independently H, halogen, haloalkyl, haloalkyloxy or alkyl;

R* is independently H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R` is independently H, $-CO_2R''$, -CONHR'', CR''O, $-SO_2NR''$, $-NR''-CO-$haloalkyl, $-NO_2$, $NR''-SO_2-$haloalkyl, $-NR''-SO_2-$alkyl, $-SO_2-$alkyl, $-NR''-CO-$alkyl, -CN,

alkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R`` is independently hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, OR^6, or NHR^7;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl, or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl, or aryl;

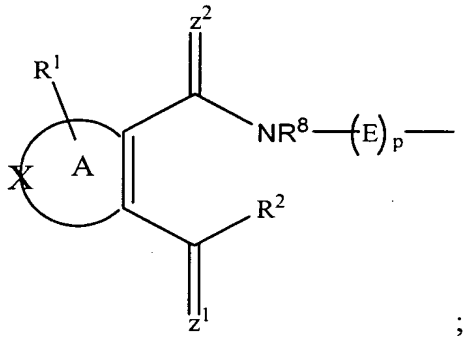
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group which is substituted by $[D_m—(CHR_3)_n]_qY$ or a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system and which contains at least one aromatic ring or



;

m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

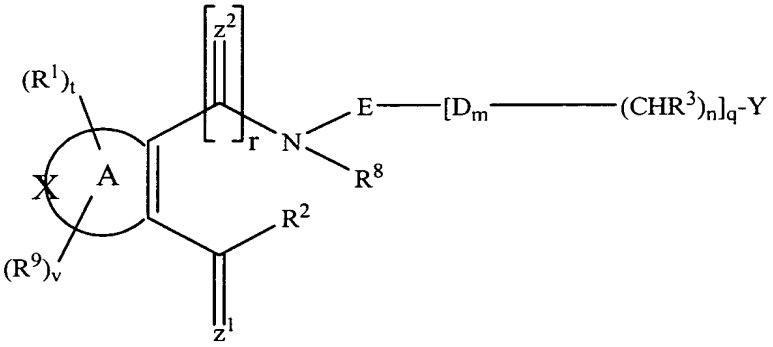
r is 0 or 1;

q is 0 or 1;

t is 1 to 3; and

v is 0 to 3.

Claim 2 (Currently Amended): A compound of the general formula (Ia) or a salt or a physiologically function derivative thereof,



(Ia)

wherein

A is a non-heterocyclic non-aromatic ring system containing 4, 5, 6, 7 or 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring represented by X may be carbonyl (C=O);

D is O, S, SO_2, NR^4, or CH_2;

[[Z]] z^1 and [[Z]] z^2 are, independently, O, S, or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy $-CO_2R``$, $-SO_3H$, -OH, $-CONR^*R``$, $-CR``O$, $-SO_2-NR^*R``$, $-NO_2$, $-SO_2-R``$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $--NR``-CO_2-R`$, $-NR``-CO-R^*$, $-NR``-SO_2-R`$, $-O-CO-R^*$, $-O-CO_2-R^*$, $-O-CO-NR^*R``$; cycloalkyl, alkylamino, hydroxyalkylamino, - SH, heteroaryl, or alkyl;

R* is independently H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R` is independently H, $-CO_2R``$, $-CONHR``$, $CR``O$, $-SO_2NR``$, $-NR``-CO-$haloalkyl, $-NO_2$, $NR``-SO_2-$haloalkyl, $-NR``-SO_2-$alkyl, $-SO_2-$alkyl, $-NR``-CO-$alkyl, -CN, alkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R`` is independently hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is NHOH or R^2 together with the nitrogen atom which is attached to R^8 form a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]$, and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, alkoxy, O-aryl; O-cycloalkyl, halogen; aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl; S-cycloalkyl, arylalkyl, or haloalkyl;

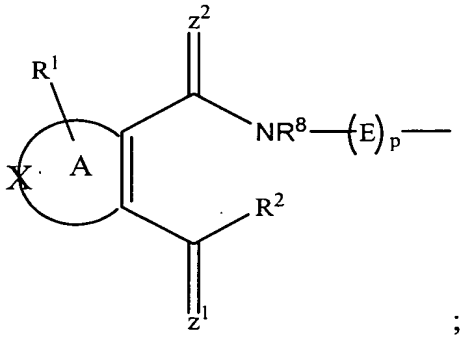
R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

R^8 is hydrogen, or alkyl;

E is an alkyl or cycloalkyl group which is substituted by $[D_m—(CHR_3)_n]_qY$or a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring or



;

m is 0 or1;

n is 0 or 1;

p is 0 or 1;

r is 0 or 1;

q is 0 or 1;

s is 0 to 2; and

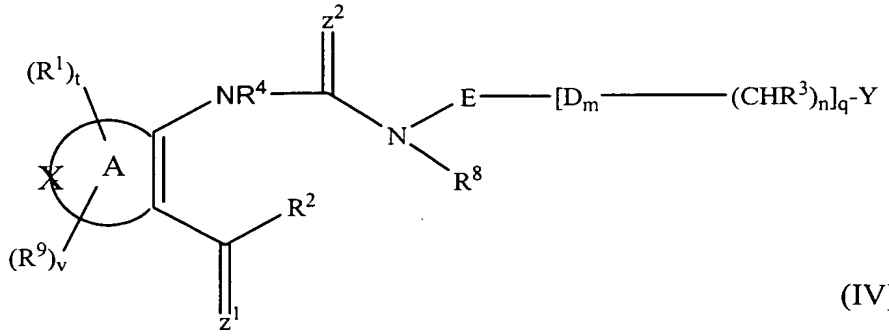
t is 0 to 3;

with the proviso that the following compounds are excluded:

compounds wherein ring A is an unsubstituted carbocycle containing six carbon atoms and one double bond between the CZ^1 and CZ^2-substituents, [[Z]] z^1=[[Z]] z^2=O, and s is 0; 1,3,5-Tribenzyl-2,4,6-trioxopyrrolo[3,4-d]imidazole, 1,3-Dibenzyl-5-(4-methoxybenzyl)-2,4,6-trioxopyrrolo[3,4-d]imidazole, 1,3-Bis-(4methoxybenzyl)-5-benzyl-2,4,6-trioxopyrrolo[3,4-d]imidazole, and 1,3-Tris-(4-methoxybenzyl)-2,4,6-trioxo-pyrrolo[3,4-d]imidazole.

Claim 3 (Canceled).

Claim 4 (Currently Amended): A compound of the general formula (IV) or a salt or physiologically functional derivative thereof,



(IV)

wherein

A is a non-heterocyclic, non-aromatic ring system containing 4, 5, 6, 7 or 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring represented by X may be carbonyl (C=O);

D is O, S, SO_2, NR^4, or CH_2;

[[Z]] z^1 and [[Z]] z^2 are, independently, O, S, or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy $-CO_2R``$, $-SO_3H$, -OH, -CONR*R``, -CR``O, $-SO_2$-NR*R``, $-NO_2$, $-SO_2$-R``, -SO-R*, -CN, alkoxy, alkylthio, aryl, -NR``-C02-R`, -NR``-CO-R*, -NR``-SO2-R`, -O-CO-R*, - O-CO2-R*, -O-CO NR*R``; cycloalkyl, alkylamino, hydroxyalkylamino, heteroaryl, -SH, or alkyl;

R* is independently H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R` is independently H, $-CO_2R``$, -CONHR``, CR``O, $-SO_2NR``$, -NR``-CO-haloalkyl, $-NO_2$, NR``-SO_2-haloalkyl, -NR``-$SO_2$-alkyl, $-SO_2$-alkyl, -NR``-CO-alkyl, -CN, alkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R`` is independently hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H or OR^6, NHR^7, NR^7OR^7 or R^2 together with the nitrogen atom which is attached to R^8 form a 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_8$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, alkoxy, O-aryl; O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl; S-cycloalkyl, arylalkyl, or haloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

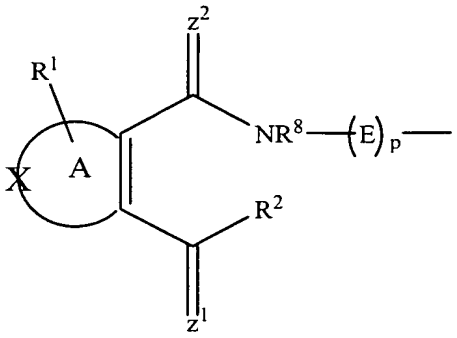
R^6 is H, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, OH, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen, or alkyl;

E is an alkyl or cycloalkyl group which is substituted by $[D_m—(CHR_3)_n]_qY$ or a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which contains at least one aromatic ring or



m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

s is 0 to 2; and

t is 0 to 3;

with the proviso that the following compounds are excluded: 5,5-Dimethyl-4-phenyl-2-(3-phenyl-ureido)-4,5-dihydro-furan-3-carboxylic acid methyl ester, 2[3-(4-Chlorophenyl-ureido)]-5,5-dimethyl-4-phenyl-4,5-dihydro-[[ftiran]] furan-3-carboxylic acid methyl ester, 2[3-(4-Methoxylphenyl-ureido)]-5,5-dimethyl-4-phenyl-4,5-dihydro-furan-3-carboxylic acid methyl ester, 2[3-(4-Methylphenyl-ureido)]-5,5-dimethyl-4-phenyl-4,5-dihydro-[[fume]] furan-3-carboxylic acid methyl ester, 2[3-(4-Nitrophenyl-ureido)]-5,5-dimethyl-4-phenyl-4,5-dihydro-furan-3-carboxylic acid methyl ester, 4-(4-Chlorophenyl)-5,5-dimethyl-2-(3-phenyl-ureido)-4,5-dihydro-furan-3-carboxylic acid methyl ester, 4-(4-Chlorophenyl)-2[3-(4-chlorophenyl-ureido)]-5,5-dimethyl-4,5-dihydro-furan-3-carboxylic-[[aeid]] acid methyl ester, 4-(4-Chlorophenyl)-2[3-(4-m[[o]]ethoxyphenyl-ureido)]-5,5-dimethyl-4,5-dihydro-furan-3-carboxylic acid methyl ester, 4-(4-Chlorophenyl)-2 [3-(4-methylphenyl-ureido)]-5,5-dimethyl-4,5-dihydro-furan-3-carboxylic acid methyl ester, or 4-(4-Chlorophenyl)-2[3-(4-nitrophenyl-ureido)]-5,5-dimethyl-4,5-dihydro-furan-3-carboxylic acid methyl ester.

Claim 5 (Previously Presented): A pharmaceutical composition comprising:

the compound of claim 1; and

a pharmaceutically acceptable diluent or carrier.

Claim 6 (Previously Presented): A pharmaceutical composition comprising:

the compound of Claim 2, and

a pharmaceutically acceptable diluent or carrier.

Claims 7-18 (Cancelled)

Claim 19 (Previously Presented): A method for treating a disease associated with the expression of dihydroorotate dehydrogenase ("DHODH") comprising administering an amount of the compound of Claim 1 effective to inhibit the activity of DHODH to a subject in need thereof.

Claim 20 (Previously Presented): A method for treating a disease associated with the expression of DHODH comprising administering an amount of the compound of Claim 2 effective to inhibit the activity of DHODH to a subject in need thereof.

Claim 21 (Previously Presented): The method of Claim 19, wherein the disease is selected from the group consisting of rheumatism, an acute immunological disorder, an autoimmune disease, a disease caused by malignant cell proliferation, an inflammatory disease, a disease that is caused by a protozoal infestation, a disease that is caused by a viral infection, *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma and athropathy.

Claim 22 (Previously Presented): The method of Claim 19, comprising administering a compound of the general formula (I) or a salt thereof.

Claim 23 (Previously Presented): The compound of Claim 1, which is compound of the general formula (I) in free form.

Claim 24 (Previously Presented): The compound of Claim 1, which is a salt of a compound of general formula (I).

Claim 25 (Previously Presented): The compound of Claim 1, which is a physiologically functional derivative of a compound of general formula (I).

Claim 26 (Previously Presented): The compound of Claim 1, wherein ring A contains five carbon atoms.

Claim 27 (Previously Presented): The compound of Claim 1, wherein ring A contains a single double bond between the carbon atoms carrying substituents Cz^1 and Cz^2.

Claim 28 (Previously Presented): The compound of Claim 1, wherein ring A contains a single X group which is carbonyl (C=O).

Claim 29 (Previously Presented): The compound of Claim 1, wherein none of the carbon atoms is replaced by X, which is carbonyl.

Claim 30 (Previously Presented): The compound of Claim 1, wherein R^1 is OH, OCH_3, SH, CO_2H, SO_3H or tetrazole.

Claim 31 (Previously Presented): The compound of Claim 1, wherein R^9 is H.

Claim 32 (Currently Amended): The compound of Claim 1, wherein R^2 is [[OH or]] OR^6.

Claim 33 (Previously Presented): The compound of Claim 1, wherein R^8 is H or methyl.

Claim 34 (Previously Presented): The compound of Claim 1, wherein Y is optionally substituted phenyl.

Claim 35 (Previously Presented): The compound of Claim 1, wherein D is S or O and m = 1.

Claim 36 (Previously Presented): The compound of Claim 1, wherein z^1 and z^2 are both O.

REMARKS/ARGUMENTS

Claims 1, 2, 4-6 and 19-36 have been allowed. Minor typographical errors in Claims 1, 2, and 4 have been corrected, e.g., replacing "Z" with "z" and in Claim 4 correcting the misspellings of "furan", "acid" and "methyl". Claim 32 has been revised to remove the redundant term "OH", since when R^2 is OR^6, it may be –OH since H is one selection of R^6. No new matter has been added and in view of the nature of the changes, no new search is required.

CONCLUSION

The Applicants respectfully request entry of the corrections presented in the Amendment above prior to issuance of this application as a patent.

Respectfully submitted,

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